RESEARCH

FGF-21 levels in polyuria-polydipsia syndrome

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Abstract

The pathomechanism of primary polydipsia is poorly understood. Recent animal data reported a connection between fibroblast growth factor 21 (FGF-21) and elevated fluid intake independently of hormonal control by the hormone arginine-vasopressin (AVP) and osmotic stimulation. We therefore compared circulating FGF-21 levels in patients with primary polydipsia to patients with AVP deficiency (central diabetes insipidus) and healthy volunteers. In this prospective cohort study, we analyzed FGF-21 levels of 20 patients with primary polydipsia, 20 patients with central diabetes insipidus and 20 healthy volunteers before and after stimulation with hypertonic saline infusion targeting a plasma sodium level ≥150 mmol/L. The primary outcome was the difference in FGF-21 levels between the three groups. Baseline characteristics were similar between the groups except for patients with central diabetes insipidus being heavier. There was no difference in baseline FGF-21 levels between patients with primary polydipsia and healthy volunteers (122 pg/mL (52,277) vs 193 pg/mL (48,301), but higher levels in patients with central diabetes insipidus were observed (306 pg/mL (114,484); P=0.037). However, this was not confirmed in a multivariate linear regression analysis after adjusting for age, sex, BMI and smoking status. Osmotic stimulation did not affect FGF-21 levels in either group (difference to baseline: primary polydipsia −23 pg/mL (−43, 22); central diabetes insipidus 17 pg/mL (−76, 88); healthy volunteers −6 pg/mL (−68, 22); P=0.45). To conclude, FGF-21 levels are not increased in patients with primary polydipsia as compared to central diabetes insipidus or healthy volunteers. FGF-21 therefore does not seem to be causal of elevated fluid intake in these patients.

Key Words

- FGF21
- diabetes insipidus
- primary polydipsia
- osmotic stimulation
- copeptin

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Introduction

Polyuria polydipsia syndrome is a common problem in clinical practice with the two main entities being primary polydipsia and central diabetes insipidus (1). While the pathomechanism of central diabetes insipidus is well known (insufficient vasopressin (AVP) secretion from the pituitary (2, 3, 4)), the cause of primary polydipsia (with excessive fluid intake often without obvious cause) remains unclear.

Fibroblast growth factor 21 (FGF-21) is a peptide hormone synthesized by several organs (e.g. liver, brown adipose tissue, muscle, pancreas). It is involved in the regulation of energy homeostasis and triggered by metabolic stress (5, 6). Thus, the main focus on FGF-21 to date is due to its involvement in the metabolic syndrome. Recently, several studies indicated a correlation between FGF-21 levels in humans with age, BMI, fat mass and

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insulin resistance (7, 8, 9) as well as smoking status (10, 11). As exogenous administration of FGF-21 induces weight loss, it is currently evaluated as a new treatment for obesity (12, 13, 14).

Recent animal studies highlighted a different field of FGF-21 research and proposed a connection between FGF-21 and elevated fluid intake (15, 16, 17). Thereby, mice with elevated FGF-21 levels had a strong preference for water instead of sweetened fluids or alcohol (16). Exogenous injection of FGF-21 led to increased water intake without recruitment of the common pathway AVP/renin-angiotensin system, meanwhile a high salt diet or water deprivation did not induce FGF-21 production (15). A similar study (17) confirmed those findings in mice, however indicating that the increased fluid intake was secondary to an elevated urine output. This suggests an FGF-21-triggered pathway in the regulation of fluid homeostasis, independent of the known AVP release upon osmotic stimulation.

Whether FGF-21 levels are increased in patients with primary polydipsia providing a possible new pathomechanism for this disorder has, to our knowledge, not yet been evaluated. The primary goal of this study was therefore to compare FGF-21 levels in patients with primary polydipsia as compared to patients with a complete lack of AVP (i.e. central diabetes insipidus) and to healthy volunteers. Secondly, we aimed to assess the effect of osmotic stimulation with hypertonic saline infusion upon FGF-21 levels.

Materials and methods

Study design and participants

Twenty patients with primary polydipsia and 20 patients with complete central diabetes insipidus from the prospective multicenter CODDI study (18) and 20 healthy volunteers from the prospective multicenter CoNORM study (19) undergoing an osmotic stimulation test with hypertonic (3%) saline infusion between 2013 and 2017 were included. Patients were randomly selected, healthy volunteers were age and BMI matched to patients with primary polydipsia. Full details of the studies rationales, designs and statistical analyses have been published elsewhere (18, 19). Both studies were registered on ClinicalTrials.gov (NCT01940614 / NCT02647736). They were approved by the Ethical Committee Northwest and Central Switzerland, University of Basel, Basel, Switzerland and the Ethical Committee of the University of Würzburg, Würzburg, Germany. Consent has been obtained from each patient or participant after full explanation of the purpose and nature of all procedures used.

Eligible patients were aged 18 years or older and had confirmed primary polydipsia or complete central diabetes insipidus. Patients with glucosuric polyuria, electrolyte disorders, untreated or insufficiently replaced pituitary-, adrenal- or thyroid deficiency, impaired kidney function, heart failure, uncontrolled hypertension or a history of epilepsy were ineligible.

Healthy volunteers were aged 18 years or older and normonatremic. Exclusion criteria included a history or presence of polyuria-polydipsia syndrome, any chronic or therapy-requiring diseases, chronic alcohol consumption or drug intake (except oral contraception).

Pregnancy or breastfeeding was an exclusion criterion in both studies.

Test protocol

No food intake was allowed after midnight, no fluid intake after 6:00 h on the test day. Diuretic or antidiuretic medications were discontinued for at least 24 h, smoking and alcohol were prohibited for at least 12 h before the test. Participants then underwent the hypertonic saline infusion test between 8:00 h and 11:00 h. After an initial 250 mL bolus, infusion of 3% saline was administered at an infusion rate of 0.15 mL per kg bodyweight per minute. Sodium levels were controlled every 30 min with venous blood gas analysis. Blood samples for the measurement of plasma osmolality, sodium, copeptin (CT-proAVP – a stable and reliable surrogate marker for AVP (1)) and FGF-21 were obtained at baseline and as soon as sodium levels reached ≥150 mmol/L.

Laboratory measurements

Blood samples for plasma osmolality and sodium were processed as routine laboratory measurements. Blood samples for copeptin and FGF-21 analysis were taken into EDTA tubes, immediately centrifuged at 4°C and stored at −80°C until central batch analysis. Plasma copeptin was then measured by a commercial automated immunofluorescence assay (B.R.A.H.M.S KRYPTOR Copeptin proAVP, Thermo Scientific Biomarkers). FGF-21 analysis was performed on the Simple Plex Ella microfluidic platform (Protein Simple, CA, USA) using detection antibodies based on the human FGF-21 quantikine ELISA (R&D systems). The coefficients of variation for the FGF-21 assay were reported as follows: intra-assay CV 8.2%, inter-assay CV 7.8%.

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Statistical analysis

The full analysis set included 60 subjects who completed the whole procedure. Results are shown as median and interquartile range (IQR) and number and percentage (%) unless stated otherwise. The Mann–Whitney *U* test was applied for two group comparisons of continuous variables. The Kruskal–Wallis test was applied for three group comparisons of continuous data. Correlation between baseline and stimulated FGF-21 with patients' characteristics and laboratory values were computed using the Spearman's Rank Correlation coefficient. Univariate linear regression models were used to assess the influence of diagnosis, age, BMI, sex and smoking status on FGF-21 levels. To adjust for these as confounding factors, a multiple linear regression model was performed.

Statistical analyses were performed using the statistic programs GraphPad PRISM version 7.03 and R statistical Software (MathSoft, Seattle, WA, USA). All hypothesis testing were two-tailed and *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics are shown in Table 1.

As the groups were age and BMI matched, there was no statistical difference between baseline characteristics in patients with polydipsia and healthy volunteers (primary polydipsia: median age 31.5 years (IQR 23.3, 47.3), BMI 24.5 kg/m^2 (IQR 22.5, 26.1); vs healthy volunteers: age 30 years (IQR 23.3, 43.8), BMI 24.7 kg/m^2 (IQR 22.5, 26.1)), but patients with central diabetes insipidus were slightly older and had a higher BMI (median age 43.5 years (IQR 28.5, 49), BMI 29.0 kg/m^2 (IQR 23.2, 30.9)). Around two-thirds were female participants (primary polydipsia 65%, central diabetes insipidus 75%, healthy volunteers 60%), the percentage of smokers was similar between the three groups (primary polydipsia 25%, central diabetes insipidus 20%, healthy volunteers 20%).

At baseline and after osmotic stimulation, plasma sodium and osmolality were significantly higher in patients with central diabetes insipidus compared to patients with primary polydipsia and healthy volunteers (Table 1). Copeptin levels were low in patients with central diabetes insipidus with no change upon osmotic stimulation, while they increased significantly in the other two groups (Fig. 1A and Table 1).

There was a statistically significant difference in baseline FGF-21 levels between all three groups, indicating

Table 1 Baseline characteristics.

	Central diabetes insipidus (n=20)			Primary polydipsia (n=20)			Healthy volunteers (n=20)			Differences between the groups *P* value	
Age, years	43.5 (28.5, 49)			31.5 (23.3, 47.3)			30.0 (23.3, 43.8)			0.15	
BMI, kg/m^2	29.0 (23.2, 30.9)			24.5 (22.5, 26.1)			24.7 (22.5, 26.1)			**0.015**	
Sex (female), *n* (%)	15 (75)			13 (65)			12 (60)			0.60	
Active smokers, *n* (%)	4 (20)			5 (25)			4 (20)			0.90	
Laboratory values	**Baseline**	**Stimulated**	***P* value**	**Baseline**	**Stimulated**	***P* value**	**Baseline**	**Stimulated**	***P* value**	**Baseline**	**Stimulated**
P-sodium, mmol/L	143 (141, 146)	154 (152, 155)	**<0.0001**	141 (139, 142)	150 (149, 154)	**<0.0001**	140 (138, 142)	153 (151, 154)	**<0.0001**	**0.009**	**0.008**
P-osmolality, mmol/kg	293 (286, 297)	313 (302, 317)	**<0.0001**	286 (280, 291)	303 (300, 308)	**<0.0001**	292 (285, 298)	314 (309, 318)	**<0.0001**	**0.012**	**0.002**
P-copeptin pmol/L	1.8 (1.3, 2.0)	1.7 (1.5, 2.0)	0.93	4.4 (2.4, 4.9)	18.7 (10.4, 23.2)	**0.0008**	4.4 (2.7, 6.6)	29.6 (26.6, 38.5)	**<0.0001**	**<0.0001**	**<0.0001**
P-FGF-21 pg/mL	306 (114, 484)	213 (133, 445)	0.45	122 (52, 277)	183 (121, 248)	0.44	193 (48, 301)	169 (63, 384)	0.39	**0.037**	0.28

Values are shown as medians (interquartile range) or as numbers (%). Two group comparison were performed using the Mann–Whitney-U test, three group comparison were performed using the Kruskal–Wallis test. Statistically significant variables are highlighted in bold.
BMI, body mass index; FGF-21, fibroblast growth factor 21; *n*, number; P, plasma.

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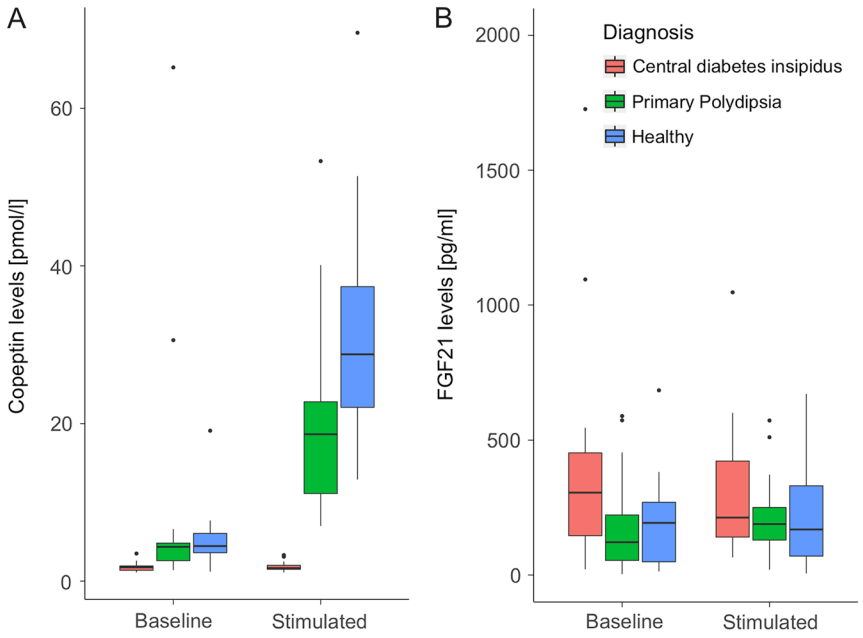

Figure 1
(A) Copeptin levels before and after osmotic stimulation with hypertonic saline infusion. (B) FGF-21 levels before and after osmotic stimulation with hypertonic saline infusion. Values shown as box plots with the middle line representing the median, the boxes the 25th to the 75th percentile and the whiskers 1.5 of the interquartile range, dots representing outliers.

higher baseline FGF-21 levels in patients with central diabetes insipidus (primary polydipsia 122 pg/mL (IQR 52, 277), central diabetes insipidus 306 pg/mL (IQR 114, 484) and healthy volunteers 193 pg/mL (IQR 48, 301); *P* value 0.037). However, this effect was not confirmed after adjusting for age, sex, BMI and smoking status in a multivariate linear regression analysis (Table 2).

Osmotic stimulation did not affect FGF-21 levels in either group (difference to baseline: primary polydipsia −23 pg/mL (IQR −43, 22); central diabetes insipidus 17 pg/mL (IQR −76, 88); healthy volunteers −6 pg/mL (−68, 22); *P*=0.45) (Figs 1B and 2). No correlation was found for baseline or stimulated FGF-21 levels with plasma sodium, -osmolality, -copeptin levels nor age, BMI or amount of daily fluid intake (data not shown).

Table 2 Univariate and multiple linear regression analysis for baseline FGF-21 levels.

	Univariate linear regression analysis		Multivariate linear regression analysis	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Central DI[a]	521 (−17 to 1060)	0.063	371 (−173 to 915)	0.19
Healthy[a]	12 (−526 to 550)	0.069	61 (−173 to 915)	0.81
Age	16 (−3 to 36)	0.118	2 (−19 to 23)	0.86
Sex: male	−114 (−594 to 366)	0.643	−119 (−573 to 333)	0.61
BMI	65 (5–124)	**0.036**	56 (−10 to 123)	0.11
Smoking yes	684 (163–1206)	**0.013**	760 (246–1274)	**0.005**

[a]Reference to primary polydipsia. Statistically significant variables are highlighted in bold.
BMI, body mass index; DI, diabetes insipidus; FGF-21, fibroblast growth factor 21; Healthy, healthy volunteers.

Discussion

We here show for the first time the course of FGF-21 levels in patients with primary polydipsia, central diabetes insipidus and healthy volunteers before and after osmotic stimulation. Our main finding is that there is no difference in FGF-21 levels between patients with excessive fluid intake and hypotonic polyuria possessing different functionality of antidiuretic AVP activity and between healthy volunteers.

Despite being a common disorder, the pathomechanism of primary polydipsia is still poorly understood. An association between mental disorders and polydipsia has been described (20, 21, 22), but a recent evaluation of 82 patients with primary polydipsia revealed a prevalence of mental diseases in only 27% (18). Although baseline copeptin – the stable surrogate marker for AVP (1) – is often osmotically suppressed in patients with primary polydipsia, the osmotic sensitivity of AVP-dependent antidiuresis is preserved in these patients as shown here and in previous studies (18, 23). Thus, the osmotically sensitive AVP system is functionally intact and alternative mechanisms must be responsible for the development of primary polydipsia. One interesting candidate to be addressed is the FGF-21 system. As shown in animal studies, elevated FGF-21 levels and exogenous FGF-21 application result in elevated water intake and diuresis respectively (15, 16, 17). Interestingly, in our study, we found no difference in FGF-21 levels between patients with primary polydipsia and central diabetes

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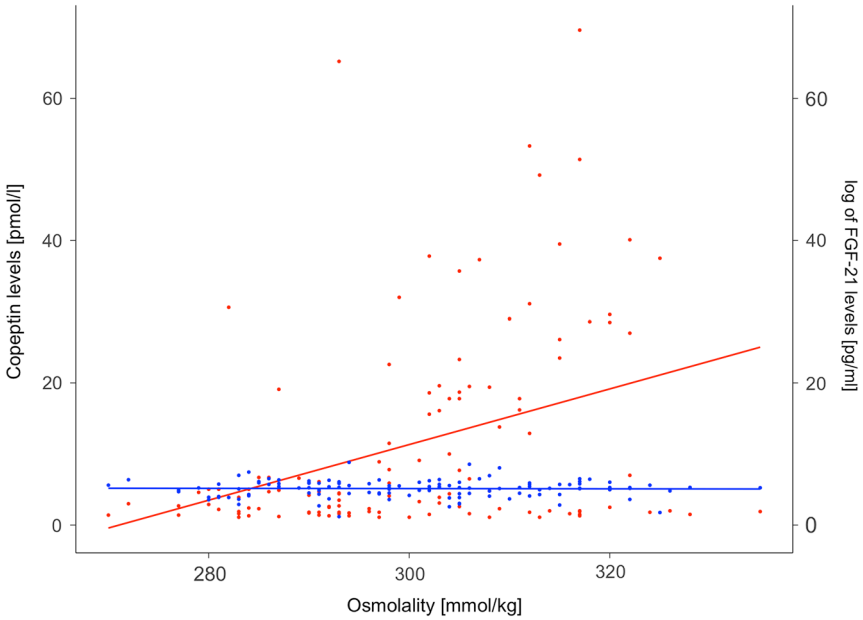

Figure 2
Correlation between FGF-21, copeptin and osmolality. FGF-21 levels (blue), copeptin levels (red) of all participants. The line representing correlation with plasma osmolality.

insipidus nor healthy volunteers. FGF-21 therefore seems not to be causal of elevated fluid intake in patients with primary polydipsia.

In agreement to the published animal data (15), osmotic stimulation did not lead to an increase in FGF-21 levels in any of the studied groups. There was also no correlation with either plasma sodium, –osmolality or –copeptin levels. In case of FGF-21 playing a role in fluid homeostasis, it seems to be working independently of osmotic control. To further investigate this question, it would be of interest to evaluate the impact of exogenous FGF-21 on fluid intake in humans. Unfortunately, this information is missing in published data (24, 25, 26).

In line with previous findings (5, 8, 9, 10), FGF-21 levels in our study were influenced by BMI and smoking habits but independent of sex. Age did not affect the results, but this could be due to the small age differences in our cohort.

The following limitations have to be mentioned. First, this was an exploratory study including 60 participants from three different groups which increased the variance in results. However, as patients were carefully selected and had confirmed central diabetes insipidus or primary polydipsia, the results should be very representative. Second, patients with central diabetes insipidus were slightly heavier and older compared to patients with primary polydipsia and healthy volunteers. We tried to adjust for this bias by multiple linear regression analysis.

In conclusion, we here show that FGF-21 levels are not higher in patients with primary polydipsia than in patients with central diabetes insipidus or than in healthy volunteers. Therefore, it is unlikely that FGF-21 is the cause of elevated fluid intake in patients with primary polydipsia. Clinical studies in humans with exogenous FGF-21 are needed to further investigate its possible role as an AVP-independent stimulator of polyuria and polydipsia.

Declaration of interest
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